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10/032,996	12/27/2001	David Botstein	GNE.2930R1C3	9529

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/032,996	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27,28 and 32-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27,28 and 32-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 27, 28 and 32-34 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility.

The current claims are drawn to a genus of nucleic acids which encode a protein termed Pro-539 (SEQ ID NO: 7) or portions thereof, in the specification, which have at least 95% amino acid sequence identity to SEQ ID NO: 7.

Credible Utility

Following the requirements of the Utility Guidelines (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for Utility.), the first inquiry is whether a credible utility is cited in the specification for use of the proteins. The cited utilities in the specification include overexpression in cancer. These utilities are credible.

Upon identification of credible utilities, the next issue is whether there are any well established utilities for the PRO 539 polypeptide. A review of the specification and of the prior art finds no well established utilities for unknown proteins whose activity, whose enzymatic or other biochemical function and whose cellular roles are entirely unknown and undisclosed in the specification.

The next inquiry is whether there are substantial or specific utilities for the PRO 539 protein of SEQ ID NO: 7 which are identified in either the specification or in the prior art.

Substantial utility

Here, the evidence in the specification provided is that the nucleic acid which encodes the PRO 539 protein is overexpressed in cancer cells. The level of overexpression of PRO 539 was minimal, not even a two fold overexpression in any cell type. Further, no statistical data was presented to show that the overexpression was significant in any way, with no P-value or other statistical measure to demonstrate that the overexpression was a real effect and not simply produced by chance.

Abundant art supports the absence of a necessary relationship between mRNA and protein

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass 95% identical molecules, there is an abundance of evidence that very similar proteins can perform

very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression

Nine out of ten recent microarray papers show discordant protein and mRNA expression data

Nine recent papers provide much stronger evidentiary showings, showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper shows a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decresed protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

Kwong et al (Genomics (2005) 26:142-158), drawn to colorectal cancer, a disease similar to the one analyzed by Appellant, has even stronger conclusions. Kwong notes that 47 genes had valid protein and mRNA data in the 10 samples and

were selected for correlation analysis. Kwong states regarding these samples that "Only 12 of the 47 genes exhibited correlated expression at a significance level less than 0.05. Surprisingly, 13 genes had a negative correlation between mRNA and protein levels. The correlation between protein and mRNA was also compared on a sample-by-sample basis. Of the 53 samples for which data was available, mRNA and protein levels were found to be correlated at a significance level of 0.05 in only 14 samples, while 14 mRNA and proteins were negatively correlated (see page 151, column 2 to page 152, column 1). Following Kwong, it is clear that it is not more likely than not that protein and mRNA expression are correlated. In fact, Kwong supports the conclusion that it is more likely than not that there is no correlation.

Chen et al (Mol. Cellular Proteomics (2002) 304-313 notes "By comparing the mRNA and protein expression levels within the same tumor samples, we found that 17% (28/165) of the protein spots (21/98 genes) show a statistically significant correlation between mRNA and protein. (see page 311, column 1)" Chen continues a little later "The majority of protein isoforms, however, did not correlate with mRNA levles and thus their expression is regulated by other mechanisms. We also observed a subset of proteins that demonstrated a negative correlation with the mRNA expression values (see page 311, column 1)." Chen does refer to Celis (ref. 19 of Chen) who cites Orntoft et al who shows 39 out of 40 proteins correlated in expression between the mRNA and protein levels.

Conrad et al (Mol. Cell Proteomics (2005) 4(9) :1284-1296) performed an analysis on 2501 proteins of which data regarding the abundance of 1900 proteins was

aligned with nucleic acid microarray data(see page 1290, column 1). Conrad found that in this very large data set "There is little correlation between RNA and protein abundance identified and predicted by cICAT (see page 1290, column 2)."

Ginestier et al (Am. J. Pathol. (2002) 161:1223-1233) teaches at table 4 that only five out of 15 genes showed concordance. Ginestier notes "For a category of molecules we found important differences between RNA and proteine xpression levels (see page 1230, column 2)."

Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of 0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Lee et al (Biotechnology and Bioengineering) (2003) 84(7):834-841) teaches "A key feature of all the observations and a common issue raised in the discussion of such results is the lack of an obvious linear correlation between mRNA expression and protein expression (see page 834, column 2). Commenting on their own data, Lee notes "Consistent with observation in other organisms; we observed no clear

relationship between mRNA amplification and protein amplification factors for Escherichia coli (see page 838, column 1)."

Provenzani et al (Carcinogenesis (2006) 27(7) : 1323-1333) shows a comparison of total mRNAs and mRNAs in the polysomal RNA, which are the mRNAs which will undergo translation into protein (see figure 2). Provenzani points out that a difference in polysomal loading will result in a difference in protein expression that is unrelated to the amount of mRNA being expressed. Provenzani notes "In this framework, our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signalling control of translation and/or in the translational machinery itself (see page 1330, column 1)." Provenzani explains this by stating "An impliciation of this possiblity would be a lack of correlation between transcriptomic and proteomic data in teh same sample (see page 1330, column 1)." Thus, Provenzani also supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based upon polysomal loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Statistical Significance

The overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant. While the specification states "Only values that were above this cutoff ratio were determined to be significant" in paragraph 0930, there is no evidence to suggest that this overexpression is statistically significant.

Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient, so there is no evidence of record that the overexpression shown has any utility as a diagnostic or for any other purpose. Also, there is no evidence that the overexpression in the prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note

that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene. Given the absence of any evidence regarding sample size and the absence of any direct association with Pro539 and lung tumors, this gene represents noise. The prior art suggests that such genes should not be placed on the array. Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays.

Absence of tissue matched controls

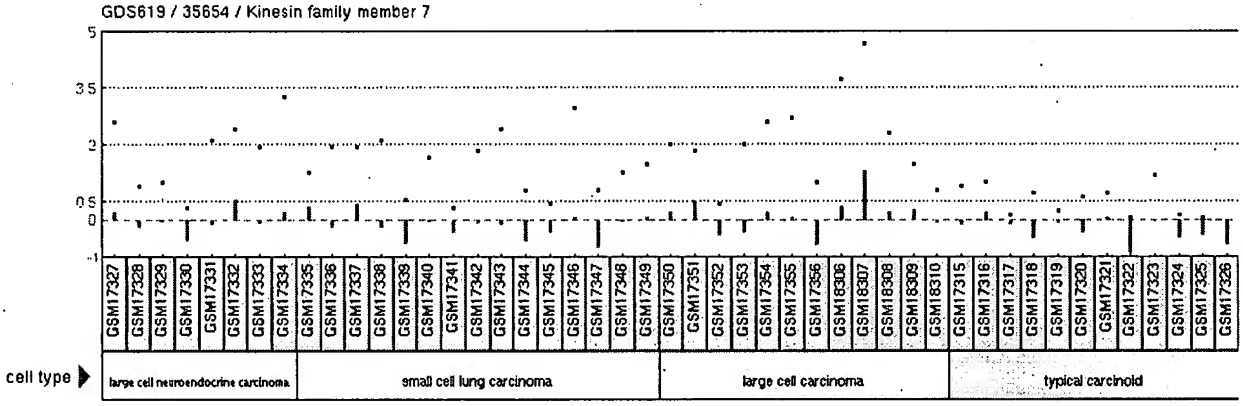
It is important to note that the gene encoding PRO539 was not found to be amplified in other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). Therefore, the overexpression data itself is questionable, since blood and lung may naturally express PRO539 at different levels. The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO1269 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

Specific data shows that Pro539 is NOT overexpressed in lung tumors.

Since the filing date of this application, a number of studies have analyzed genes to determine overexpression in lung tumors relative to normal controls. Some of these have posted the entirety of their data sets to the NCBI website at

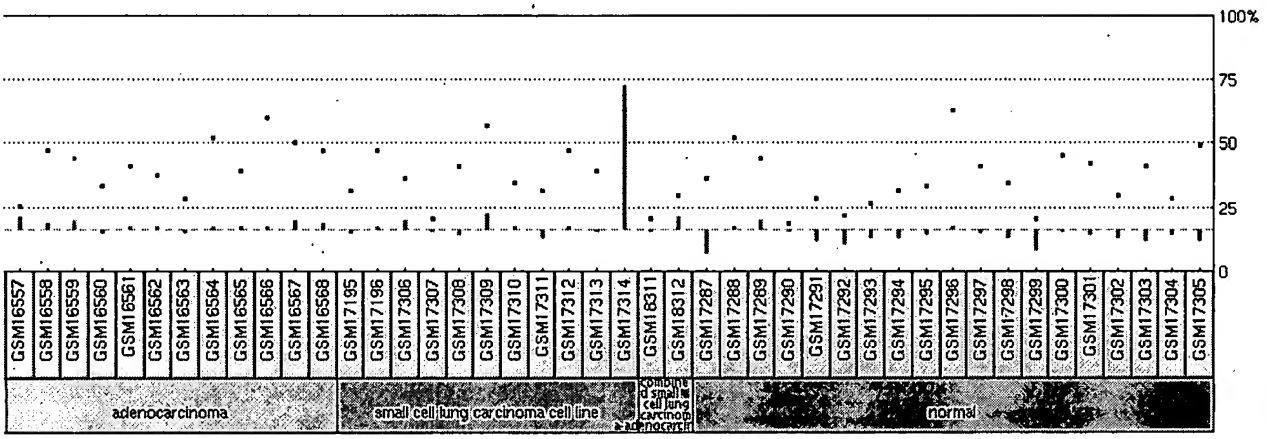
http://www.ncbi.nlm.nih.gov/geo/. Several specific analyses demonstrate that Pro539, which is known as Kif7, is not overexpressed in lung tumors. Two such analyses are shown below. As the first analysis shows (on a proprietary array), titled, Lung neuroendocrine tumor classification, the Kif7 gene expression is all over the map. There is no correlation whatsoever between expression and cancer. In the second analysis (on the U133 affymetrix array), colorectal carcinoma samples were analyzed and again, the data appears to show no relationship with cancer.

Title: Lung neuroendocrine tumor classification
Summary: Molecular classification of lung high-grade neuroendocrine tumor (HGNT) groups. Carcinoids, large-cell carcinoma, adenocarcinoma, small

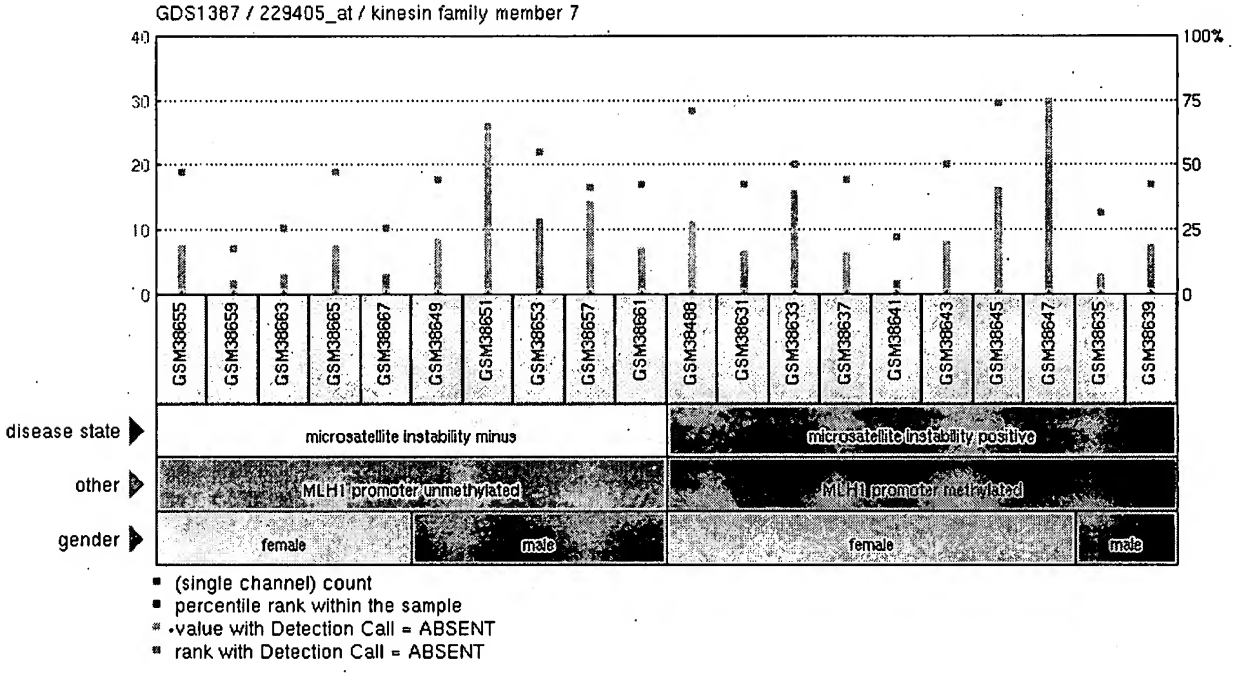


- (dual channel) log ratio
- percentile rank within the sample

l-cell lung carcinoma cell lines, and normal lung examined.



Title: Colorectal carcinoma subtype with microsatellite instability (HG-U133B)
Summary: Comparison of colorectal carcinoma specimens positive and negative for microsatellite instability (MSI). Results also cor of MMR genes results in MSI.



Therefore, given the specific data for PRO539 itself which demonstrates that in two different experiments on two different arrays with multiple samples, the nucleic acid was not overexpressed, there is no reason to believe that the protein would be overexpressed.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this case is also similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539 antibodies and proteins. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Specific Utility

In the current case, even if the substantial utility argument above were found unpersuasive, there is no specific utility given for this PRO-539 protein of SEQ ID NO: 7. The protein, as distinguished from the nucleic acid, has not been associated with any disease, any condition, or any other specific feature. There is no association of the protein with cancer or with any other disease. As the utility guideline training materials note on page 5-6, "Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed". Here, the overexpression of the nucleic acid gives no specific utility because it is entirely unrelated to uses of the protein. A protein cannot be used to detect changes in its cognate nucleic acid, as shown by the Gokman-Polar and Meric papers, where protein levels are not correlative with nucleic acid levels. Therefore, there is no specific utility for this protein until a specific ligand is identified.

Finally, with regard to the utility analysis, the current situation directly tracks Examples 4 and 12 of the utility guidelines, where a protein of entirely unknown function and a receptor with an unknown ligand was characterized as lacking utility.

Claim Rejections - 35 USC § 112 – Written Description

3. The rejection of claims 48-54 under 35 U.S.C. 112, first paragraph, is moot in view of the cancellation of these claims.

Claim Rejections - 35 USC § 112 – Scope of Enablement

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27, 28 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a PRO-539 protein which is 95-100% identical to SEQ ID NO: 7. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims broadly encompass not only the particular PRO-539 protein but also include any protein which shares 95% sequence identity to SEQ ID NO: 7.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the activity of polypeptides and nucleic acids. It would require significant study to identify the actual function of the PRO-539 protein and nucleic acid, and identifying a use for this protein would be an inventive, unpredictable and difficult undertaking in itself. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art is extremely unpredictable with regard to protein function in the absence of reliable information regarding the protein activity. Even very similar proteins, as shown by homology, may have very different functions (see Rost et al (J. Mol. Biol. (2002) 318(2):595-608). In the current case, where no specific information is known regarding the function of the protein in actual biological organisms, it is entirely unpredictable what function and activity will be found for this protein. The prior art does not resolve this ambiguity, since no prior art activity is identified for the protein.

Abundant art supports the absence of a necessary relationship between mRNA and protein

This data further lacks any of the hallmarks of utility because the overexpression of the nucleic acid is not relevant to the utility of the protein. There is no evidence that

the protein itself is overexpressed. Meric et al (Molecular Cancer Therapeutics (2002) 1:971-979) in a discussion of regulation of gene activity in cancer notes that "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation and protein stability (page 971, column 1)." So Meric teaches that there is not necessarily a correlation between mRNA levels and protein levels in cancer cells, since the regulation may occur at levels other than that of the mRNA, such as in the level of translation of the mRNA or in the stability of the protein.

The absence of any necessary correlation between increased mRNA levels and increased protein levels is made explicit by Gokman-Polar (Cancer Research (2001) 61:1375-1381) who teaches "Quantitative reverse transcription-PCR analysis revealed that PKC mRNA levels do not directly correlate with PKC protein levels, indicating that PKC isozyme expression is likely regulated at the posttranscriptional/translational level (see abstract)." Gokman-Polar show in figures 6 and 7 that there is no increase in mRNA expression for any of the isozymes, while the protein is significantly overexpressed as shown by figures 4 and 5. This demonstrates that there is no relationship between mRNA levels and protein levels.

A further evidentiary showing is provided by Pennica et al (Proc. Natl. Acad. Sci. USA (1998) 95:14717-14722) who shows that WISP-2 DNA was amplified in cancer cells but was actually demonstrated REDUCED RNA expression (see abstract). This provides additional evidence that there is no relationship between gene amplification and mRNA levels, since mRNA levels have no necessary correlation with gene amplification.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Further, given the breadth of these claims which encompass 95% identical molecules, there is an abundance of evidence that very similar proteins can perform very different functions. For example, Rost et al (J. Mol. Biol. (2002) 318(2):595-608) notes regarding assignment of enzymatic activity based upon homology comparisons that "The results illustrated how difficult it is to assess the conservation of protein function and to guarantee error-free genome annotations, in general: sets with millions of pair comparisons might not suffice to arrive at statistically significant conclusions (abstract)." Thus, even high levels of homology do not necessarily correlate with actual protein function. In the current case, where the function of PRO-539 (SEQ ID NO: 7) is not known, the expectation is even lower that there is any utility that can be derived based upon the sequence.

This situation is extremely similar to example 12 of the Utility Guidelines, where a protein which was known to be a receptor, but where the ligand was unknown, was found to lack utility. In the current case, the putative PRO-539 protein, lacks any substantial utility whatsoever, and solely relies upon an small level of mRNA overexpression in cancer cells. However, there is no necessary relationship between the protein levels or utilities and such an overexpression of the nucleic acid. So this

case is similar to the receptor in Example 12, since it lacks a substantial utility because there is no "real world" context of use. Further research would be required to identify and reasonably confirm a "real world" context of use for PRO-539. As noted in the utility guidelines, basic research on a product to identify properties and intermediate products which themselves lack substantial utility are all insubstantial utilities (see page 6 of the Utility guideline training materials).

Protein and DNA Microarray data shows no necessary correlation between mRNA overexpression and protein expression

Nine out of ten recent microarray papers show discordant protein and mRNA expression data

Nine recent papers provide much stronger evidentiary showings, showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper shows a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing genes, Czupalla continues "In contrast, a second group of 70 gene products comprises those for which we did not observe any changes in mRNA expression although we could clearly detect either increased or decresed protein expression by 2-DE (see page 3874, column 1)." The data of Czupalla, which

addresses 117 genes, shows that it is more likely than not in this data set that there is no correlation between mRNA expression and protein expression. This supports the conclusion that mRNA expression cannot be relied upon for enablement and utility of the protein since no necessary correlation exists.

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Conrad et al (Mol. Cell Proteomics (2005) 4(9) :1284-1296) performed an analysis on 2501 proteins of which data regarding the abundance of 1900 proteins was aligned with nucleic acid microarray data(see page 1290, column 1). Conrad found that in this very large data set "There is little correlation between RNA and protein abundance identified and predicted by cICAT (see page 1290, column 2)."

Ginestier et al (Am. J. Pathol. (2002) 161:1223-1233) teaches at table 4 that only five out of 15 genes showed concordance. Ginestier notes "For a category of molecules we found important differences between RNA and proteine xpression levels (see page 1230, column 2)."

Anderson et al (Electrophoresis (1997) 18:533-537) shows that for 19 proteins that were compared between 2D gel electrophoresis and mRNA analysis "the correlation coefficient obtained over this set of data was 0.48. This number is intriguingly close to the middle position between a perfect correlation (1.0) and no correlation whatever (0.0) (see page 536, column 1)." In fact, the correlation is slightly closer to showing that there is no correlation whatsoever between protein and mRNA data. This is consistent with the showing of Washburn (Proc. Natl. Acad. Sci. (2003) 100 (6):3107-3112, who analyzed a comparison of 678 loci and found a correlation of

0.45 (see page 3109, column 1), which also shows a correlation that is closer to the absence of correlation than to a positive correlation.

Lee et al (Biotechnology and Bioengineering) (2003) 84(7):834-841) teaches "A key feature of all the observations and a common issue raised in the discussion of such results is the lack of an obvious linear correlation between mRNA expression and protein expression (see page 834, column 2). Commenting on their own data, Lee notes "Consistent with observation in other organisms, we observed no clear relationship between mRNA amplification and protein amplification factors for Escherichia coli (see page 838, column 1)."

Provenzani et al (Carcinogenesis (2006) 27(7) : 1323-1333) shows a comparison of total mRNAs and mRNAs in the polysomal RNA, which are the mRNAs which will undergo translation into protein (see figure 2). Provenzani points out that a difference in polysomal loading will result in a difference in protein expression that is unrelated to the amount of mRNA being expressed. Provenzani notes "In this framework, our analysis shows that 80% of the genes undergoing a gene expression change in the transition between SW480 and SW620 cells do it by varying their degree of polysomal loading, implying a dramatic subversion in the signalling control of translation and/or in the translational machinery itself (see page 1330, column 1)." Provenzani explains this by stating "An impliciation of this possiblity would be a lack of correlation between transcriptomic and proteomic data in teh same sample (see page 1330, column 1)." Thus, Provenzani also supports the conclusion that up to 80% of genes will not show differential expression based upon mRNA level, but rather based upon polysomal

loading, so that mRNA level will not provide significant information regarding the utility, or lack thereof, for the protein.

So not only is there no necessary connection between the level of protein in a cell and the amount of mRNA, but there is also no necessary correlation between the amount of DNA in a cell and the amount of mRNA. Therefore, any evidence by Applicant showing overexpression of one component does not provide utility for the protein itself.

Statistical Significance

The overexpression data does not provide a substantial utility for several reasons. First, there is no showing that the overexpression was statistically significant and correlated with any diagnostic utility. The absence of such a diagnostic utility is particularly striking since there is no evidence that the overexpression effect was statistically significant. While the specification states "Only values that were above this cutoff ratio were determined to be significant" in paragraph 0930, there is no evidence to suggest that this overexpression is statistically significant.

Further, there is no evidence that the overexpression was reproducible. From the data presented in the specification, a single prostate tumor sample from a single patient may have been used. Such a result from a single patient would not support any utility because even if the nucleic acid was overexpressed in the one patient, there would be no expectation that the result would appear in even one other patient, so there is no evidence of record that the overexpression shown has any utility as a diagnostic or

for any other purpose. Also, there is no evidence that the overexpression in the prostate tumor was anything other than a nonspecific effect due to the presence of an exogenous protein in the mixture.

Further, the art supports the conclusion that many genes are irrelevant in gene microarray assays. As Li et al (J. Theoretical Biology (2002) 219:513-551) note "The presence of this power law function prevents an intrinsic cutoff point between "important" genes and "irrelevant" genes (see abstract)." Li continues in the text to note that "In a typical microarray experiment, however, the problem is not that one does not put enough genes on a chip, but rather having too many genes (see page 539, column 1)." This concept that genes whose expression does not change is irrelevant is not limited to Li. Ding et al (Bioinformatics (2003) 19(10):1259-66) notes "A two-way ordering of gene expression data can force irrelevant genes toward the middle in the ordering and can thus be discarded (See abstract)." So Ding expressly indicates that genes without change in expression profiling (and Ding's preferred embodiment is cancer genes) should be discarded. Ding notes at page 1259 that in a selection from thousands of genes, 50 are sufficient. Similarly, Sawiris et al (Cancer Research (2002) 62:2923-2928) notes "One of the advantages of specialized arrays is that they do not include irrelevant genes that may contribute to noise during data analysis (see page 2923, column 2)." Thus, the overwhelming state of the art supports the position that many genes are irrelevant, that genes whose expression does not change are noise, and that these irrelevant genes are so insignificant that ideally they are not placed on the arrays or used at all. The current gene, Pro539, is such a gene. Given the absence

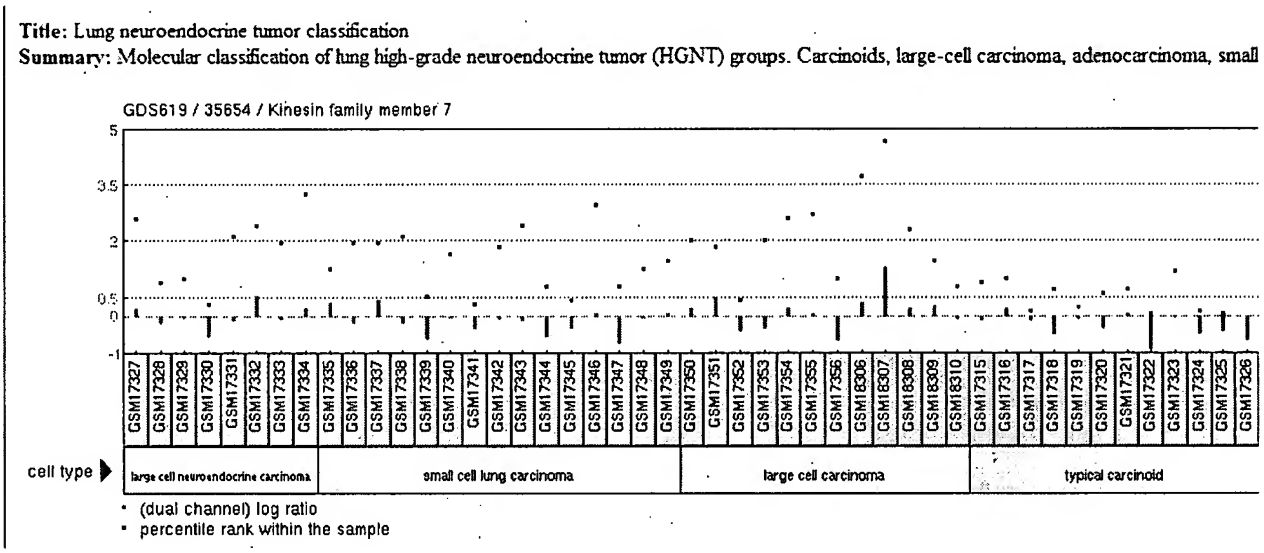
of any evidence regarding sample size and the absence of any direct association with Pro539 and lung tumors, this gene represents noise. The prior art suggests that such genes should not be placed on the array. Therefore, genes such as Pro539, lack substantial utility as useful on gene expression arrays.

Absence of tissue matched controls

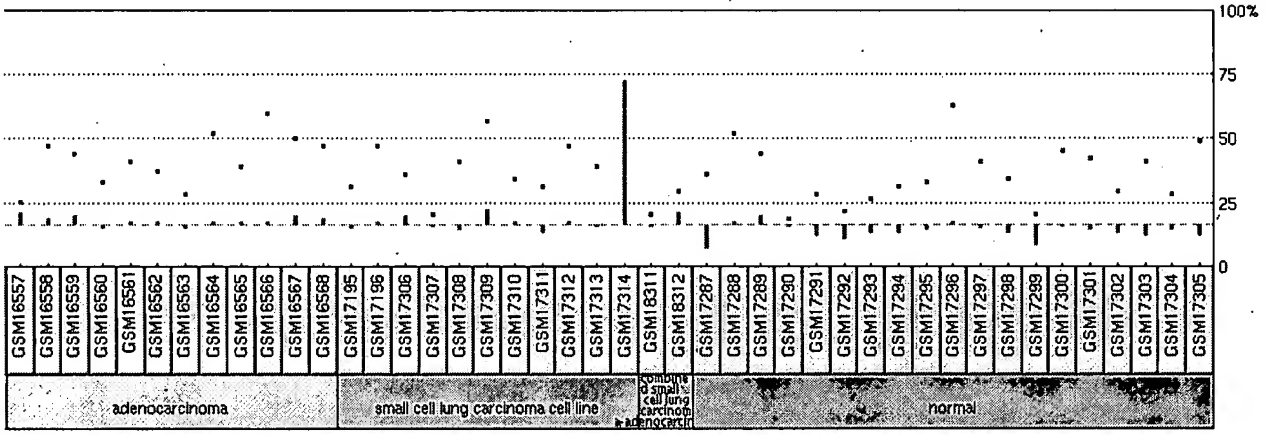
It is important to note that the gene encoding PRO539 was not found to be amplified in other listed tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 115). Therefore, the overexpression data itself is questionable, since blood and lung may naturally express PRO539 at different levels. The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy. Given these details, one skilled in the art would not conclude that the gene encoding PRO1269 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Gokman-Polar.).

Specific data shows that Pro539 is NOT overexpressed in lung tumors.

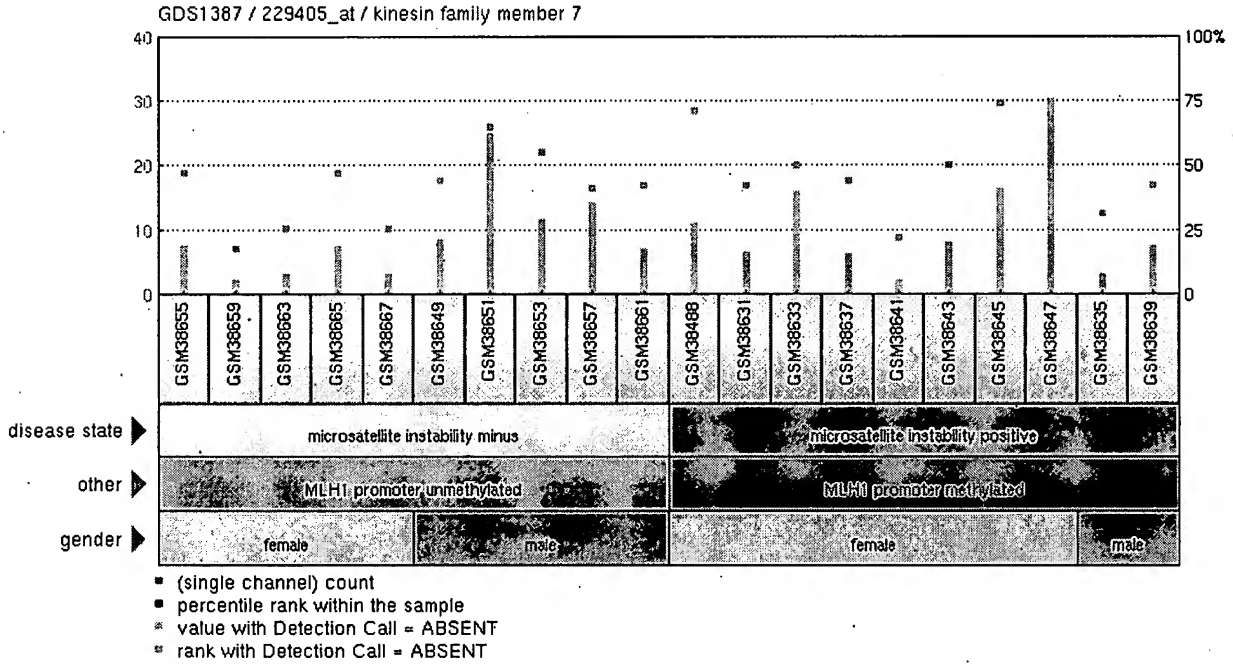
Since the filing date of this application, a number of studies have analyzed genes to determine overexpression in lung tumors relative to normal controls. Some of these have posted the entirety of their data sets to the NCBI website at http://www.ncbi.nlm.nih.gov/geo/. Several specific analyses demonstrate that Pro539, which is known as Kif7, is not overexpressed in lung tumors. Two such analyses are shown below. As the first analysis shows (on a proprietary array), titled, Lung neuroendocrine tumor classification, the Kif7 gene expression is all over the map. There is no correlation whatsoever between expression and cancer. In the second analysis (on the U133 affymetrix array), colorectal carcinoma samples were analyzed and again, the data appears to show no relationship with cancer.



l-cell lung carcinoma cell lines, and normal lung examined.



Title: Colorectal carcinoma subtype with microsatellite instability (HG-U133B)
Summary: Comparison of colorectal carcinoma specimens positive and negative for microsatellite instability (MSI). Results also cor of MMR genes results in MSI.



Therefore, given the specific data for PRO539 itself which demonstrates that in two different experiments on two different arrays with multiple samples, the nucleic acid was not overexpressed, there is no reason to believe that the protein would be overexpressed.

Working Examples

The specification has no working examples that relate to the protein. The nucleic acid working examples, showing overexpression in certain cancer cell lines, are not relevant for the reasons given above. Specifically, there is no statistical showing that the overexpression of the nucleic acids is even significant in any way. Even if the nucleic acid data is deemed significant, there is no showing that the results from nucleic acids have any correlation with the protein and the art cited above demonstrates that there is no presumption of such a correlation..

Guidance in the Specification.

The specification provides no specific or substantial uses for the PRO-539 protein. The specification does generically teach that the protein may be used in further research, such as in generation of antibodies, but provides no specific and substantial use for the protein.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

5. Applicant's arguments filed July 23, 2007 have been fully considered but they are not persuasive.

Applicant's arguments were fully addressed in the examiner's Answer and nonfinal rejection which preceded this action. Several arguments will be readdressed in brief, for the sake of completeness.

Effect of Ex Parte Goddard

Applicant argues that the unpublished and nonprecedential decision of the Board of Patent Appeals and Interferences in the appeals 2006-1469 should control in this case. With due deference to the BPAI, the specific decision does not control for several reasons. Most importantly, the current case is factually different.

First, in 2006-1469, that examiner provided zero evidence to rebut the single declaration that argued that mRNA and protein were necessarily correlated. In the current case, there are 10 global comparison references, which address this specific issue, and nine of the ten references conclude that there is no correlation. In fact, the

art clearly teaches newly discovered abundant regulatory mechanisms which underly the differential expression of mRNA and protein. After mRNA is synthesized, the specific mRNA, and the protein expressed by it, are subjected to regulation in splicing, by microRNA and small interfering mRNA (siRNA) (the subject of the 2006 Nobel prize to Andrew Fire and Craig Mello), mRNA degradation, differential protein expression in the ribosome, protein degradation, among many levels of regulation. Each of these subsequent levels of regulation will result in differences between mRNA levels and protein levels, and this data is reflected in the 10 cited references. This significant evidence was not presented to the BPAI in 2006-1469, and therefore could not be considered by the BPAI.

Second, in 2006-1469, the examiner provided zero specific evidence to rebut the overexpression of the mRNA. In the current case, specific evidence is presented that PRO539 is NOT overexpressed in lung cancer. Specific evidence of this nature, if it existed, was not applied in 2006-1469. Consequently, contrary to Applicant's argument, there is specific evidence in this case regarding the expression of the PRO539 nucleic acid.

Third, the current application itself, along with other similar applications, with substantially more evidence than 2006-1469, were up for appeal at the same time as 2006-1469, but were withdrawn and RCEd by Applicant, not permitting a decision by the BPAI on the additional factual material presented in this application. The BPAI designated the 2006-1469 decision as "not written for publication" and stated that this opinion "is not binding precedent of the Board". Therefore, on a case with a significantly

different factual background, including specific evidence rebutting Applicant's specific gene as being overexpressed, the BPAI decision does not control the outcome of this application.

Effect of Declarations

i. The Polakis declaration demonstrates that 28 out of 31 genes are coexpressed at the RNA and protein level based upon their data. The declaration does not specifically address whether PRO539 is coexpressed and the data does not address this specific molecule.

ii. The Grimaldi declaratrion represents solely the opinion of Dr. Grimaldi. No specific evidence regarding PRO539 is adduced.

iii. Dr. Goddard's assay is not directed to this issue of protein versus mRNA expression, but rather the accuracy of Taqman in analyzing gene copy numbers, a point not at issue.

iv. Dr. Ashkenzi does not address the issue of protein versus mRNA expression, but rather argues that gene amplification is a utility. Since there is no argument by Applicant that PRO539 is increased in gene copy number, only that the mRNA is overexpressed, this argument is not relevenat to PRO539.

v. Dr. Smith's results show that in only 8 out of 26 tumors, PRO 539 is overexpressed. This does not demonstrate anything regarding the protein expression. In fact, looking at the "normalized ratio" of Dr. Smith, 1 normal lung sample out of 7 showed a ratio exceeding 2 as well as 8 out of 26 tumors. Thus, it is certainly legitimate to conclude, particularly given the GEO data cited in the rejection, that the argued

"overexpression" provides no useful result, since the levels of overexpression are present in normal as well as tumor tissues. Given the very small sample sizes, there is no reason to expect that the results from tumor are reliably different than the results from normal.

In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion.

(1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. This is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

(2) There is significant evidence which opposes the conclusion of these declaration. As noted in the rejection above, ten recent papers provide much stronger evidentiary showings, with nine showing that it is more likely than not that mRNA expression is not correlated with protein expression, while only the Orntoft paper showing a counter example. Czupalla et al (Proteomics (2005) 5:3868-3875) notes "Comparison of the results for differential expression obtained by the two techniques essentially reveals two groups of genes. The first group comprises 47 genes for which differences in mRNA expression and in abundance of the corresponding proteins spots on 2-D gels were consistently detected (see page 3873, column 2)." After discussing

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(3) All of the Declarants have an interest in the case since they are either employed by the assignee or under duties to the assignee.

(4) There is factual support based upon the data shown by Dr. Polakis and Dr. Smith, for their positions. The raw data, the number of repetitions, and the statistical analysis, if any are not presented. This makes a complete analysis of the data impossible, since the raw information underlying the conclusion is not presented.

However, given the very strong data opposing the conclusion of of the declarations, derived from nine different papers, with only one paper supporting the

position of declarants, along with the incompletely presented data, the conclusion is inescapable that there is no necessary correlation between mRNA and protein levels and that in fact, it is not likely for any given protein that such a correlation will exist. In particular, the evidence suggests that no such correlation exists for PRO539.

Effect of GEO data

Applicant attempts to minimize the GEO data by arguing that the second chart did not compare to normal and that the first had four overexpressions in tumor and none in normal. With regard to the second chart, this chart simply shows the great variation in expression of Kif7 in tumors, showin the unreliability of this marker as "useful" in any diagnostic setting.

Applicant is simply incorrect in stating that none of the controls are overexpressed. As the GEO FAQ notes "The blue squares represent the percentile ranked value of a spot compared to all other spots within that Sample. That is, all values within each Sample are rank ordered and placed into rank percentile 'bins'. This gives an indication of the relative expression level of that gene compared to all other genes on the array." Looking at the chart, it is quite evident that the blue dot of GSM7296 in the normal set has among the highest percentile expression relative to all other genes on the array. Two of the normal samples out of 19 total exceed 50% of the total genes.

Effect of the References

Applicant then attempts to address the references. Rather that accept the determination of the author of the references, as cited in the rejection, Applicant attempts to reanalyze the data to come out with different results. These arguments

were previously addressed and remain unpersuasive. The references which perform global comparisons, none of which were before the BPAI in Goddard, repeatedly note that there is no correlation between protein and mRNA expression.

Therefore, the rejections are maintained.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system; see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1637
8/1/07